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VIEWPOINT

Mesenchymal Stem Cell Therapy Can Transcend Perianal Crohn's Disease: How Colorectal Surgeons Can Help in the COVID-19 Crisis

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Introduction

While the true mortality rate from COVID-19 seems to be a moving target, rationing essential medical equipment, protecting medical personnel, and planning for maximal hospital occupancy is a real daily reality. As colorectal surgeons, we do not personally manage ventilators or cases of acute respiratory distress syndrome (ARDS), but we are faced with an imminent reality of redeployment to medical, and/or ICU care. While many of us have not intubated a patient since residency, we will undoubtedly strive to apply any medical care that is needed. Surprisingly, we may be able to also apply our knowledge of novel therapeutics to the COVID-19 crisis, finding ourselves in a position to actually help these patients, despite our focus on colorectal pathology. Mesenchymal stem cells (MSCs), which have now demonstrated safety and efficacy for perianal Crohn's disease across several phase I,¹⁻⁵ phase II,^{4,6,7} and phase III⁸ clinical trials, act as a potent anti-inflammatory and immunomodulatory agent. Just as Crohn's disease is characterized by increased inflammatory cytokines and aberrant ratios of immune cells (*ie*, decreased number of T-regulatory cells and increased proinflammatory M1 macrophages), COVID-19 patients also exhibit hyperinflammation with a cytokine storm and recruitment of immune cells that result in an ARDS picture. Thus, the purpose of this review is to help colorectal surgeons apply our experience with MSCs to COVID-19.

COVID-19 Problem

The outbreak of coronavirus (COVID-19) has led to a rapid increase in morbidity and mortality due to ARDS worldwide. ARDS is the most common complication in COVID-19 patients. This is thought to be due to a rapid cytokine cascade within a short period of time resulting in severe inflammation, which creates an increase in lung endothelial and epithelial permeability.⁹ This severe proinflammatory response results in lung damage, impaired gas exchange, and severe respiratory failure with a high mortality rate. Mortality due to severe

ARDS is high at 30-40%.¹⁰⁻¹² Despite extensive investigation of therapeutic strategies for managing ARDS, the current standard of care is largely supportive with lung-protective ventilation and a fluid conservative strategy.⁹ Despite advances in lung-protective ventilation and fluid management, a high age-related mortality rate remains.

COVID-19 infected patients who develop ARDS are typically older with comorbidities, but no age group or health-status has been spared as COVID has crossed the globe. In ARDS, severe lung inflammation is thought to be sustained by elevated proinflammatory cytokines including interleukin (IL)-6, IL 1, IL 8, tumor necrosis factor- α (TNF- α) and as noted by elevated levels of serum C- reactive protein (CRP). The mortality rate in COVID-19 related severe ARDS is quite high despite treatment with antivirals, glucocorticoids, immunoglobulins, and ventilation. Preclinical and clinical evidence indicate that MSCs migrate to the lung and respond to the proinflammatory lung environment by releasing anti-inflammatory factors reducing the proliferation of proinflammatory cytokines noted above while modulating regulatory T-cells and macrophages to promote resolution of inflammation. Therefore, MSCs have potential to increase survival in management of ARDS.

MSCs Have Actually Already Been Useful

Two studies from China have already shown MSCs to be a relevant player in the armamentarium of proposed therapeutics for COVID-19. The first was a case report of a critically ill COVID-19 patient on a ventilator who had progressed despite intensive therapy with concurrent liver injury. The patient was treated with allogeneic human umbilical cord MSCs using three intravenous infusions of 5×10^7 cells, each three days apart. Within four days of the first MSC infusion, the patient was extubated and able to walk. All measured parameters, including circulating T cell counts, returned to normal levels. No obvious side effects were observed.¹³ The second study was a study from Wuhan of 7 patients that received a single intravenous dose of MSCs at 1×10^6 cells per kilogram weight that reported

that the treatment was well tolerated, and all seven patients were able to be extubated. All treated patients had confirmed COVID-19 and had symptoms of high fever, shortness of breath, weakness, and low O₂ saturation ($\leq 95\%$) (Table 1).¹⁴ Within 2 to 4 days after MSC treatment, all symptoms disappeared, and O₂ saturation increased. Clinical improvement was presumably associated with a reduction in inflammatory cytokines as the reduction in CRP in the most severely affected patient was 191 g/L to 10.1 g/L following treatment. In addition, after the intravenous administration of MSCs, serum levels of the proinflammatory cytokine TNF- α decreased significantly, while levels of the anti-inflammatory IL-10 increased significantly in the 7 MSC-treated patients but not in the controls. All patients have since been discharged from the hospital.

Relevant Animal Studies and Human COPD and ARDS Trials Before COVID

Animal data

In a sepsis model in mice, infusion of adipose-derived MSCs into septic animals decreased the levels of proinflammatory mediators TNF- α , IL 6, IL1b, IL12, and interferon-gamma (IFN- γ), regulated the activation of expressed normal T-cells and secreted regulated upon activation, normal T-cell expressed and presumably secreted (RANTES) and macrophage inflammatory protein-2 (MIP-2)) and increased IL-10 in the main affected organs. MSC infusion also decreased inflammatory infiltration in the peritoneal cavity, lung, liver, and intestine and showed an antimicrobial effect by reducing bacterial load in the main affected organs.¹⁵ In another preclinical study in mice, MSC treatment (1×10^6 cells/animal) decreased mortality to 40% in 26 h compared to 100% in the untreated septic group, decreased inflammatory cytokines, increased IL -10 and inhibition of apoptosis of splenocytes.¹⁶ In an endotoxemic rat model, adipose-derived MSC treatment decreased the level of inflammatory cytokines in the lung and serum, reduced inflammatory changes in the lung, prevented apoptosis in the kidney, and improved multiorgan injury.¹⁷ In a mouse model

with pneumonia, MSC treatment showed reduced bacterial counts as a consequence of the release of the antimicrobial peptide LL-37 by the cells.¹⁸

Human Clinical Pneumonia, COPD, and ARDS Trials

Adipose-derived MSCs were studied for ARDS as early as 2014 in a phase I clinical trial of 20 patients (NCT01902082). The primary objective was the safety of 1×10^6 cells/kg given intravenously, and the secondary objectives were efficacy of treating ARDS. While safety was established, efficacy was limited likely due to low doses and lack of protocol optimization. Recently, a new clinical trial with the same adipose-derived MSCs (SEPCELL) for the treatment of bacterial pneumonia has been conducted (NCT03158727). While the final efficacy data of the study have not been reported, there have been as of yet no adverse events related to the MSCs. Similarly, bone marrow derived MSCs have been used in clinical trials of both chronic obstructive pulmonary disease (COPD) and ARDS. In the clinical trials of COPD, those with an elevated CRP >4 mg/dL had more significant improvements, underscoring the importance in the inflammatory pathway. Three studies have used bone marrow-derived MSCs for ARDS, which consistently report that MSCs are safe but have disparate efficacy results. A small study by Simonson et al¹⁹ administered a single infusion of 2×10^6 /kg bone marrow-derived MSCs to two patients with severe, refractory ARDS, and both patients subsequently improved respiratory and hemodynamic function and reversed multiorgan failure with subsequent discontinuation of supportive therapy and discharge from intensive care. In parallel, multiple pulmonary and systemic markers of inflammation measured in bronchoalveolar lavage fluid and blood samples improved. A later phase IIa prospective double-blind multicenter clinical trial (ClinicalTrials.gov Identifier: NCT02097641) of sixty patients with moderate to severe ARDS reported a 28-day mortality rate of 30% in the MSC-treated group compared to 15% in the placebo groups, which was a nonsignificant difference.²⁰ The authors concluded a larger trial needed to be performed. The

most results of the most recent phase IIa prospective double-blind multicenter clinical trial (ClinicalTrials.gov Identifier: NCT02611609) have not yet been published but were presented as an abstract at the American Thoracic Society Meeting in Dallas, Texas, in May 2019. The MSC group had a lower mortality than the placebo group (25% versus 40%), higher number of ventilator-free days, higher number of ICU-free days, and in more severe ARDS patients, these results were even more extreme (*i.e.*, mortality 50% versus 25%). The therapy was again well tolerated with no serious adverse events related to the treatment administration. The same product received a Fast Track Designation from the Food and Drug Administration (FDA) in May 2019, and the manufacturer's partner received an Orphan Designation to fast track their ARDS program in November 2019.²¹

Mechanism of MSCs

Immunomodulatory and anti-inflammatory capacity of mesenchymal stem cells

Several *in vitro* and *in vivo* experiments showed local and systemic immunomodulatory properties of this kind of cells. At short-term, they modulate the inflammation status, shifting from Th1 to Th2 immune response. At long term, they may restore homeostasis through generation of immune cells with regulatory phenotype like regulatory T cells (T regulatory), regulatory B cells and M2 macrophages.^{22–24} Furthermore, the activity of adipose-derived MSCs *in vivo* can be modulated through toll-like receptor (TLR) signaling.²⁵ These receptors have been linked to rejection and inflammatory diseases (eg, Crohn's disease, rheumatoid arthritis, or sepsis), because they can recognize pathogenic or autoantigenic components similar to components derived from pathogens or tissue danger signals produced by an injury. They have also been shown to promote B cell migration through the secretion of chemotactic factors.²⁶

Based on these aforementioned properties, MSCs have been used for treatment of complex fistula in patients with Crohn's disease. In this clinical setting, they have already shown efficacy in the repair and regeneration of damaged tissue and has been included in European Crohn's and Colitis Organization (ECCO) algorithm for CD.^{27,28}

The differential feature of pulmonary pathology in COVID-19 consisting of massive lung inflammation with a *cytokine storm* and an ICU mortality COVID-19 is characterized by increased IL-2, IL-7, granulocyte stimulating factor, interferon-gamma inducible protein 10, monocyte chemoattractant protein 1, macrophage inflammatory protein 1a, and tumor necrosis factor- α .²⁹ Predictors of mortality in Wuhan, China, were elevated ferritin and IL-6, suggesting might be due to a virally driven hyperinflammation. In hyperinflammation, immunosuppression is likely to be beneficial.³⁰ This is why a multicenter randomized control trial of tocilizumab (Actemra, Roche Holding AG, Basel Switzerland), an anti-IL-6 receptor monoclonal antibody was approved for COVID-19 pneumonia in China (ChiCTR2000029765). MSCs also inhibit this cytokine storm, specifically IL-1 which promotes the release of anti-inflammatory cytokines, increase T regulatory cells, and transform M1 (proinflammatory) macrophages into M2 (anti-inflammatory). Furthermore, IL-1 activates MSCs towards an anti-inflammatory, revascularization and regenerative phenotype in lung tissue.¹⁷ This is the reason why its use has been proposed in pulmonary sepsis and cystic fibrosis. These are cells that have proven to be very safe when used in a similar situation.¹⁸

While MSCs have been administered locally for perianal CD, it has been well established that MSCs get trapped in the lungs when administered intravenously and that MSCs migrate to sites of inflammation. Thus, taken together, intravenous administration of MSCs is ideally suited to treated ARDS related reaction to COVID-19.

Ongoing Trials Using MSCs to Treat COVID19 Pneumonia

Four clinical trials are actively enrolling in China using MSCs to treat lung disease after SARS-COV2 (Table 2), and we anticipate this to increase as multiple MSC international companies are working on single case emergent use, compassionate use, and phase III clinical trials to enroll shortly in the United States and Europe. Inclusion criteria are typically patients with moderate to severe ARDS without multisystem organ failure. Primary outcomes include both safety and efficacy depending on the trial design. Efficacy is most often measured as survival, ventilator-free days, and ICU-free days.

Where We Are Going

While we are not certain of the clinical efficacy of MSCs for COVID-19, there is significant data demonstrating safety. Without alternative therapeutic options in ventilated patients, MSCs offer a promising treatment alternative that targets diminishing the cytokine storm and resultant immune cell infiltrate. Even if MSCs effectively treat 50% of patients, we have won. The application of novel therapeutics should not be confined to any particular field or disease states. If we can apply what we have learned to alternative pathologies, we can expand our horizons as colorectal surgeons and put our specialty in the middle of the fight against COVID-19.

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Table 1: Characteristics and disposition of 7 COVID+ patients treated with MSCs¹⁴

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7	Contro 11	Contro 12	Contro 13
Gender	Male	Female	Female	Female	Male	Male	Male	Female	Female	Female
Age (yrs)	65	63	65	51	47	55	53	75	74	46
COVID19 Type	Severe	Severe	Severe	Common	Common	Severe	Severe	Severe	Severe	Severe
Fever °C	38.6	37.7	38.2	38.5	38.4	39	39	36	38.9	37.7
Shortness of breath	+++	+++	++	+	+	+++	+++	+++	++	+
Oxygen saturation (%)	89	93	92	95	94	92	90	91	92	93
Cough, weak, poor appetite	++	+	++	+	++	++	++	+	++	+
Time to recovery after injection (days)	3	2	2	1	1	1	1	Dead	ARDS	Stable

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Control: patients COVID19+ treated with placebo.

M: male, F: female; ARDS: acute respiratory distress syndrome.

TABLE 2. Ongoing clinical trials using mesenchymal stem cells for COVID-19.

NCT Number	Study Title	Conditions	Interventions	Phase	Study Design	Locations	Status
NCT04313322	Treatment of COVID-19 Patients Using Wharton's Jelly-Mesenchymal Stem Cells	Use of Stem Cells for COVID-19 Treatment	WJ-MSCs	Phase 1	Single Group Assignment (Open Label)	Stem Cells Arabia Amman, Jordan	Recruiting
NCT04288102	Treatment With Mesenchymal Stem Cells for Severe Corona Virus Disease 2019(COVID-19)	Corona Virus Disease 2019(COVID-19)	MSCs Saline containing 1% Human serum albumin (solution of MSC)	Phase 1 Phase 2	Randomized Parallel Assignment	Maternal and Child Hospital of Hubei Province Wuhan, Hubei, China Wuhan Huoshenshan Hospital Wuhan, Hubei, China	Recruiting
NCT04273646	Study of Human Umbilical Cord Mesenchymal Stem Cells in the Treatment of Novel Coronavirus Severe Pneumonia	2019 Novel Coronavirus Pneumonia COVID-19	UC-MSCs Placebo	Not Applicable	Randomized Parallel Assignment Masking: None (Open Label)	Union Hospital, Tongji Medical College, Huazhong University of Science and Technology Wuhan, Hubei, China	Not yet recruiting
NCT04269525	Umbilical Cord(UC)-Derived Mesenchymal Stem Cells(MSCs) Treatment for the 2019-novel Coronavirus(nCoV) Pneumonia	Pneumonia, Viral Pneumonia, Ventilator-Associated	UC-MSCs	Phase 2	Single Group (Open Label) Primary Purpose: Prevention	Zhongnan Hospital of Wuhan University Wuhan, Hubei, China	Recruiting
NCT04252118	Mesenchymal Stem Cell Treatment for Pneumonia Patients Infected With 2019 Novel Coronavirus	2019 Novel Coronavirus Pneumonia	Biological: MSCs	Phase 1	Non-Randomized Parallel Assignment Masking: None (Open Label)	Beijing 302 Military Hospital of China Beijing, China	Recruiting

Source: clinicaltrials.gov